

ORIGINAL RESEARCH

Fosfomycin Susceptibility Among Esbl-Producing Escherichia Coli Causing Community Acquired Uncomplicated Urinary Tract Infections

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ABSTRACT

Introduction: Fosfomycin has recently gained popularity due to the emergence of multi-drug resistant bacteria and its wide range of spectrum with considerable activity against both Gram-positive and Gram-negative bacteria, including E. coli.

Objective: The present study aims to evaluate the susceptibility of ESBL-producing E. coli to fosfomycin among patients suffering from UTIs.

Materials And Methods: The study included all patients who presented to the hospital's various outpatient departments (OPDs) with symptoms of UTIs. ESBL-producing E. coli was detected by using cephalosporin/clavulanate combination discs. Fosfomycin susceptibility test was done by using fosfomycin 200 µg disc. Antimicrobial susceptibility testing was done for all the ESBL-producing E. coli.

Results: A total of 266 (37.2%) isolates were found to be ESBL producers out of 714 E. coli isolates. Only 8 (3%) isolates were resistant to fosfomycin.

Conclusion: Fosfomycin has proved to be highly effective in the treatment of multidrug-resistant bacteria such as ESBL producing E. coli, and its prudent use is advised to avoid the development of resistance.

Keywords: ESBL-EC, Fosfomycin resistance, UTIs

INTRODUCTION

Urinary tract infections (UTIs) are one of the most frequent bacterial infections affecting people worldwide [1]. It is an important cause of morbidity in females of all age groups and elderly males [2]. It may be either community or hospital acquired [3]. Every year, more than 150 million people are affected by community-acquired UTIs [4]. Women have a higher risk of developing UTI than men, at a ratio of 8:1 [5]. UTIs may be classified as uncomplicated or complicated. Uncomplicated UTIs are cystitis and pyelonephritis in women with structurally and functionally normal tracts, whereas complicated UTIs are those in men, pregnant women,

or the elderly, and in patients with anatomical or functional abnormalities or those having indwelling catheters[6].

Escherichia coli is the most common pathogen causing both complicated and uncomplicated UTIs, and it accounts for up to 80% of community-acquired uncomplicated UTIs [2,7]. Extended spectrum beta lactamase (ESBL) producing *E. coli* poses a significant clinical challenge as it is associated with cross-resistance to other non-beta-lactams such as aminoglycosides, fluoroquinolones, and trimethoprim/sulphamethoxazole, in addition to resistance to penicillins, cephalosporins (including third and fourth generation) and aztreonam [8,9]. UTIs caused by ESBL-producing *E. coli* may increase both the cost of treatment and the duration of stay in the hospital [10].

Fosfomycin, a phosphoenolpyruvate analogue produced by *Streptomyces* spp., is an old bactericidal antibiotic agent. It acts by inactivating the UDP-N-acetylglucosamine 6-phosphotransferase (MurA) enzyme involved in the formation of the peptidoglycan precursor UDP N-acetylmuramic acid, the first step in the synthesis of the bacterial cell wall. It has a wide range of spectrum with considerable activity against both Gram-positive and Gram-negative bacteria, including *E. coli*. Fosfomycin has recently gained popularity due to the emergence of multi-drug resistant bacteria and its ability to inhibit adhesion of *E. coli* in the bladder wall, high concentrations achieved in urine, and highly effective single dose therapy [11].

The present study aims to evaluate the susceptibility of ESBL-producing *E. coli* among the patients attending the OPD due to symptoms related to UTIs in order to establish the role of fosfomycin as the antibiotic of choice for empirical therapy in cases of uncomplicated UTIs in our health care set up.

MATERIALS AND METHODS

The present study is a descriptive study conducted over a one-year period from April 2018 to March 2019 in the Department of Microbiology, Mayo Institute of Medical Sciences, Barabanki, Uttar Pradesh. The study included all patients who presented to the hospital's various outpatient departments (OPDs) with symptoms of UTIs.

SELECTION CRITERIA OF STUDY POPULATION

Patients attending the OPDs with symptoms of UTIs such as urgency, frequency, burning micturition and fever were included in the study. The exclusion criteria are as follows:

- a. History of hospitalization in last two weeks
- b. Known congenital anomaly of urinary tract
- c. Antibiotic intake in last two weeks
- d. Vaginal bleeding
- e. Antibiotic intake in last two weeks

SAMPLE COLLECTION AND PROCESSING

About 30-50 ml of 'clean catch' mid-stream urine was collected from each study participant in a sterile wide-mouthed container of 100 ml capacity with a lid. Sample was immediately transported to the bacteriology laboratory and cultured within 2 hours of collection on CLED & MacConkey agar and incubated at 37°C in aerobic environment for 24 hours. The plates were examined after 24 hours of incubation for growth. In case of no growth obtained the plates were further incubated. The culture were considered negative only after completion of 48 hours of incubation. Microscopic examination of uncentrifuged urine samples was done for detection of pus cells, epithelial cells, crystals, fungal elements and RBCs. The growth obtained were further identified as *E. coli* by standard laboratory protocol.

DETECTION OF ESBL-PRODUCING *E. COLI*

This was performed by using cephalosporin/clavulanate combination discs as per Clinical Laboratory Standards Institute (CLSI) guidelines. Cefotaxime (30 µg) and ceftazidime (30 µg) discs with and without clavulanate (10 µg) were used for performing the test. A lawn culture of *E. coli* was done on Mueller-Hinton agar (MHA) and discs were placed at an appropriate distance in the medium and plates were incubated overnight at 37°C in aerobic environment. A ≥ 5 mm increase in the zone of inhibition for both cefotaxime and ceftazidime with clavulanate vs the zone of inhibition for both without clavulanate indicates ESBL-producing *E. coli*. *Klebsiella pneumoniae* ATCC 700603 and *E. coli* ATCC 25922 were used as quality control for this test.

FOSFOMYCIN SUSCEPTIBILITY TESTING

This was done by Kirby–Bauer disk diffusion method by using fosfomycin 200µg disc as recommended by the CLSI guidelines. A lawn culture of *E. coli* was done on MHA and fosfomycin disc was placed on the surface and plates were incubated aerobically at 37°C for 16-18 hours. The interpretation of result was done as per CLSI guidelines.

ANTIMICROBIAL SUSCEPTIBILITY TESTING OF ESBL PRODUCING *E. COLI*

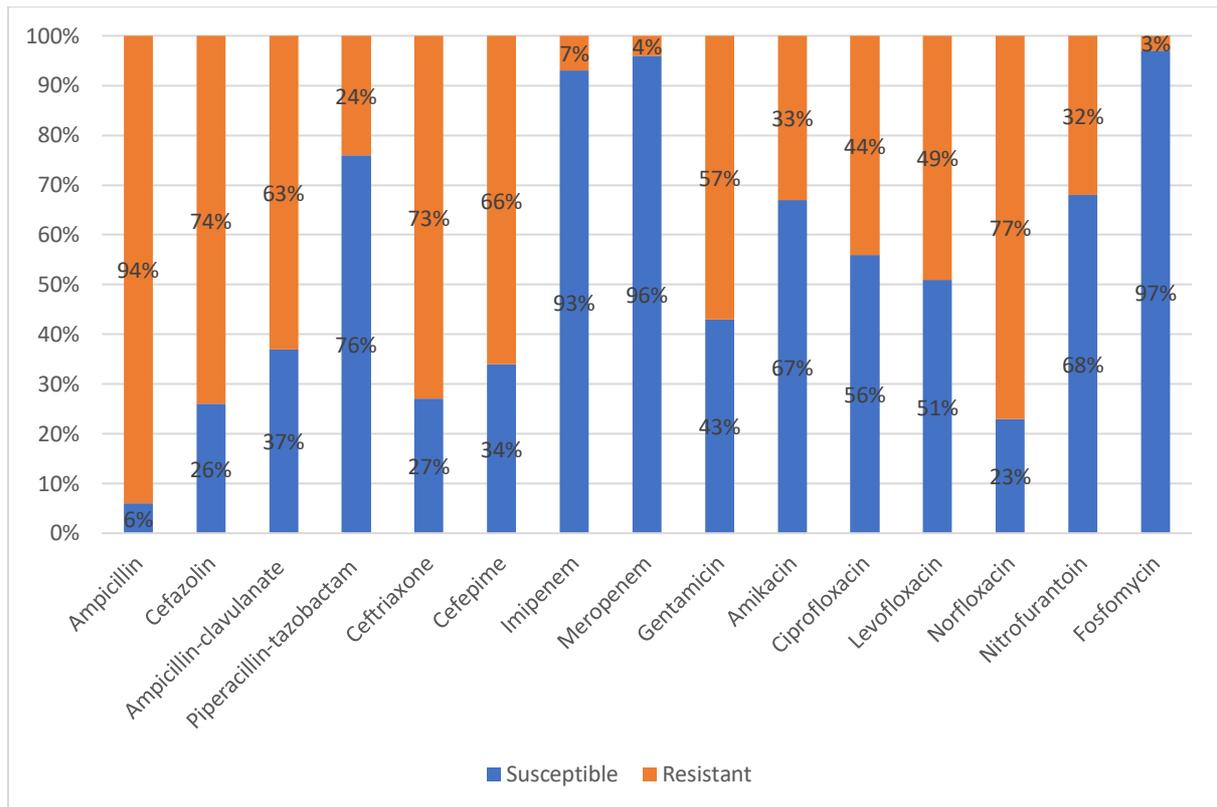
It was performed by Kirby–Bauer disk diffusion method. Following antibiotic discs were used: Ampicillin (10µg), cefazolin (30 µg), ceftriaxone (30 µg), cefepime (30 µg), ampicillin-clavulanate (20/10 µg), piperacillin-tazobactam (100/10 µg), imipenem (30 µg), meropenem (30 µg), gentamicin (10 µg), amikacin (10 µg), ciprofloxacin (5 µg), levofloxacin (5 µg), norfloxacin (10 µg), nitrofurantoin (300 µg).

RESULTS

A total of 714 non-duplicate *E. coli* isolates were obtained from the urine samples of the patients included in the study. Among them, 266 (37.2%) isolates were found to be ESBL producing *E. coli*. Out of 266 isolates, 179 (67.3%) and 87 (32.7%) were isolated from female and male patients, respectively.

The antimicrobial susceptibility profile of ESBL-producing *E. coli* is depicted in Figure 1. It showed a higher susceptibility to meropenem (96%), imipenem (93%), nitrofurantoin (68%), and amikacin (67%). Only 7% of ESBL producing *E. coli* were resistant to fosfomycin.

Figure 1: Antimicrobial susceptibility profile of ESBL producing *E. coli*



DISCUSSION

UTIs are one of the most prevalent illnesses seen in outpatient settings. *E. coli*, the most frequent causative agent of UTIs, has been found to be resistant to most of the routinely used antibiotic agents. With the increasing prevalence of ESBL-producing *E. coli*, the antibiotic options are very limited [2]. Fosfomycin has been shown to be highly effective in treating uncomplicated UTIs, and its use has recently increased.

In our study, we have found that 37.2% isolates of *E. coli* were ESBL producers. The high prevalence of ESBL *E. coli* may be attributed to irritational use of antibiotics commonly used for treatment of UTIs. Various authors have found a varying prevalence depending on the geographical distribution of ESBL producers, as shown by Dawoud et al (56.4%), Kumar D et al (55.5%), Rezai MS et al (30.5%), Rimal U et al (25.5%), Chander A et al (13.5%) [9,12-15]. In this study, we found a higher prevalence of UTIs among females than males, which is consistent with the findings of various studies [2].

The antimicrobial susceptibility profile showed a higher resistance to ampicillin (94%), norfloxacin (77%), cefazolin (74%), and ceftriaxone (73%). Whereas, moderate resistance was found against gentamicin (57%), levofloxacin (49%), ciprofloxacin (44%), amikacin (33%), and nitrofurantoin (32%). Meropenem (96%), and imipenem (93%) were highly effective against ESBL producers. Similar findings were observed by Halabi et al, which showed 100% resistance to ampicillin, approximately 90% resistance to third and fourth generation cephalosporins, and 41% to gentamicin and 19% to amikacin. They have also found carbapenems were very effective against ESBL-producing *E. coli* [16].

Fosfomycin was found to be the most effective against ESBL-producing *E. coli*, with only 3% of isolates resistant to it in our study. Several authors reported similar findings, with resistance rate ranging from 2.4% to 6.7% [17-20]. Though the use of fosfomycin for the treatment of uncomplicated UTIs has lately grown, resistance is not particularly widespread, which may be ascribed to rational use of the antibiotic.

CONCLUSION

The emergence of resistance to antibiotics commonly used for the treatment of urinary tract infections has significantly increased the number of patients visiting outpatient departments. Multidrug resistant bacteria are a major challenge to clinicians and their burden has increased lately. Fosfomycin has proved to be highly effective in the treatment of multidrug-resistant bacteria such as ESBL-producing *E. coli*, and its prudent use is advised to avoid the development of resistance.

CONFLICT OF INTEREST

None to declare

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